International Journal of Physics
and Research (IJPR)
ISSN(P): 2250-0030; ISSN(E): 2319-4499
Vol. 3, Issue 5, Dec 2013, 11-20

RADIATION DOSIMETRIC PROPERTIES OF NEW OXA-, THIADIAZOLE, TRIAZOLE AND THIAZOLE QUINAZOLINE DERIVATIVES

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ABSTRACT

There is a need to synthesis a new TL material has a simple glow curve, glow peak and tissue equivalent suitable to study the biological effects of ionizing radiation. New 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives of 4-thiomethyl-quinazoline have been synthesized by cyclization of hydrazide, amidrazone and thiosemicarbazide derivatives via their treatments with carbon disulfide, sulfuric acid, sodium hydroxide, and mercuric oxide. 1,3-Thiazole derivatives were prepared from thiosemicarbazide and arylidene derivative after its treatment with ethylchloroactate, phenacyl bromide and mercaptoacetic acid. The radiation dosimetric properties of new 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazole and 1,3-thiazole derivatives of 4-thiomethyl-quinazoline have been investigated. The TL-radiation response was found to be sensitive to the compound composition quantitatively and qualitatively due to different created trap centers according to the type of doping oxides. The therapeutic range (0.5 to 2 Gy) of the TL response versus the delivered dose without reaching saturation level provides a possibility to use this material in a phantom for checking the treatment plans of the dose delivery in the near future. The TL enhancement response to gamma radiation makes the substance doped with **11**system a promising material for gamma detection dosimetry. These properties may have important applications in developing selective detectors and dosimeter suitable to study the biological effects of exposure to ionizing radiation.

KEYWORDS: Biomaterial, TL-Dosimetry, Therapeutic Doses

INTRODUCTION

Thermoluminescence (TL) studies have received considerable attention especially, the structures of the defects giving rise to TL glow peaks [1,2]. On the other hand, the previous observations have shown that LiF:Mg,Ti really presents a rather complex TL mechanism from a solid state point of view [3]. Therefore, there is no general agreement on the authentic structure of defects in LiF:Mg,Ti and there is a still lack of understanding of TL mechanism of this material [4].

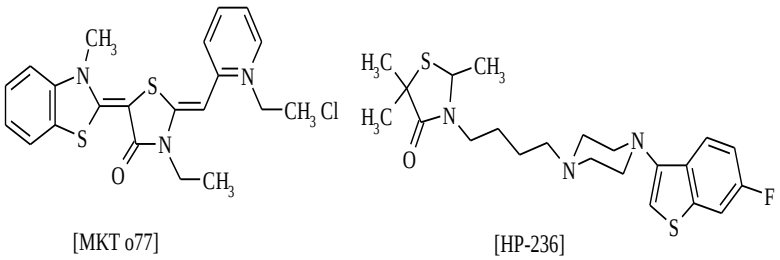
The dosimetric and TL properties of LiF:Mg,Ti used as a reference material for comparison are disreputable variable and non-universal [5,6]. This is in part due to its very complex glow curve with its many glow peaks reported between room temperature and 400^0C under various conditions of dose, annealing and storage parameters, LET of the radiation field, etc. Each glow peak may have distinctly different dosimetric characteristics and the relative intensity of the various glow peaks depends on a great many factors. However, the dosimetric characteristics of the glow peaks rather than the glow curve (integration over a number of glow peaks) will surely lead to better understanding of TLD and contribute to the adoption of better dosimetric technique. So, there is a need to synthesis a new TL material has a simple glow curve and glow peak.

A great deal of research work on electron rich nitrogen heterocycles has been done to identify new compounds, having potential applications in photonics. Such compounds class is very attractive since they could be prepared in different

shapes and sizes and can accept rare earth ions without inducing any crystallization. These classes are very attractive since they could be prepared in different shapes and sizes and can accept rare earth ions without inducing any crystallization. They are promising materials for photonics applications because of wide transmissions window, good stability and durability, high-refractive index, higher non-linear optical properties, and relatively low-phonon energies. Although the benefits of radiation are enormous and continuously increasing, it is well known that ionizing radiation can induce cancer and genetic defect. Such compounds have good ability to host luminescent activators. It was reported that thermoluminescence TL for derivatives of such classes has been archived [7]. Recently, some studies achievedfor uses of solar cells in dosimetry ‘monocrystalline silicon solar cell of the construction n+pp++ Passivated Emitter Solar Cell (PESC) was irradiated by ^{60}Co gamma ray doses. The TL enhancement response to gamma radiation makes the monocrystalline silicon solar cell system a promising material for gamma detection dosimetry[8]. inorganic dosimetry showed Ruthenium phthalocyanineterial of gamma-ray thermoluminscence dosimeterhas a potential use as a material for gamma – raythermoluminscence dosimeter(TLD) for clinical dosimetery[9].

Also, Dosimetric properties of the quaternary tellurite glasses have been measured as a function of Different compositions of the glassy system in different rare earth oxides concentration by using thermoluminescence(TL) detection technique.The experiment results showed that tellurite investigation of thermoluminescence has a potential use as the materials of gamma-ray thermoluminescence [10]. Besides that, The behavior of the different types of tellurite glasses is analyzed regarding to their kinetic parameters and luminescence emission which enhances the claim of tellurite glasses for use as TLD material at therapeutic radiation doses [11]. Sulfonated grafted polymers also provided a better understanding of the response to ^{208}pb ions irradiation to determine the importance of grafting conversionin accurate dosimetric properties measurement [12].

On the other hand, quinazoline derivatives are an important class of nitrogen-containing heterocycles which display a wide variety of biological activities [13] and the quinazoline moiety is an important part of many natural alkaloids. Compounds with diverse biological activities (hypotonic, antiallergic, antibacterial and anthelminthic) have been found among quinazoline derivatives [14]. Most biologically active quinazolines possess substituents at C-2 and N-3 positions. The anti fungal, antibacterial, anti-HIV activities of Schiff and Mannich bases derived from isatin and *N*-[4-(4-chlorophenyl)thiazol-2-yl]thiosemicarbazide [15], antimicrobial activity of fluorinated hydroquinazoline derivatives [16] and 6-chloro-2-morpholino 4-quinazolyl-5-nitro-2-furyl hydrazone [17] were reported. On this basis, we have synthesized some derivatives of quinazoline semicarbazone. It has been reported that, certain compounds bearing 1,3,4-oxa-, thiadiazole, and 1,2,4-triazole nucleus possess significant anti-inflammatory activity [18,19]. Some 1,2,4-triazole derivatives incorporating Schiff base structure were synthesized as antitumor agents [20]. Compounds MKT 077 [21] and HP-236 [22] are thiazole compounds and have been reported as a registered antitumour and antipsychotic agents, respectively (Figure 1).



[MKT o77] [HP-236]

Figure 1: Structure of MKT077 and HP-236

Owing to the above facts and in continuation of our research program [17-20] in the synthesis of biologically active 1,3,4-oxadiazol, 1,2,4-triazol, 1,3,4-thiadiazol, our goal here in the synthesis of such heterocyclic compounds and thiazolidinone nuclei attached to the quinazoline-thiomethyl derivative and investigation of the luminescence spectra of the prepared compounds in addition to structure correlation.

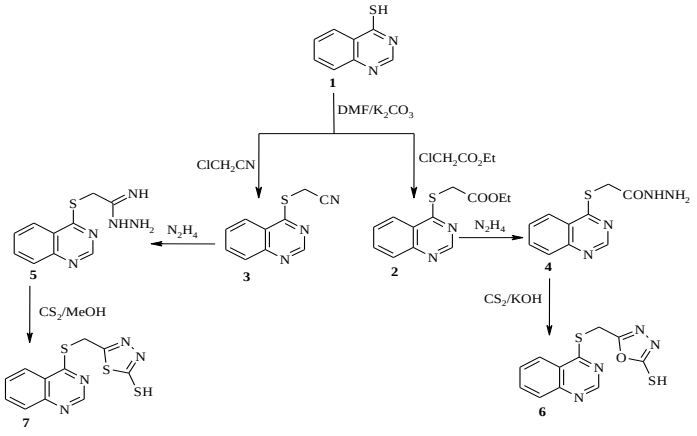
EXPERIMENTAL

The reading out process was performed using a TLD reader (Model 4500, Bicron/Harshaw) equipped with two photomultiplier tubes, which could record luminescence independently. The reader was controlled by WinREMS Software supplied with the spectrometer and running on a Windows® computer. The thermoluminescence detectors TLD-100 were used with dimensions of 3.2 X 3.2 X 0.89 mm^3 and doped with titanium (11.5 ppm) and magnesium (300 ppm) purchased from Bicorn / Harshow Chemical Company. Solvents and reagents were obtained from Acros (Geel, Belgium), Fluka (Taufkirchen, Germany) or Sigma (Steinheim, Germany). All melting points were measured on Electro thermal IA 9000 series digital melting Point apparatus. The IR spectra were recorded in potassium bromide discs on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. The NMR Spectra were recorded at 270 MHz on a Varian Mercury VX-300 NMR spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) were run in deuterated chloroform ($CDCl_3$) or dimethylsulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass Spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro analytical Centre of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F254, Merck).

RESULTS AND DISCUSSIONS

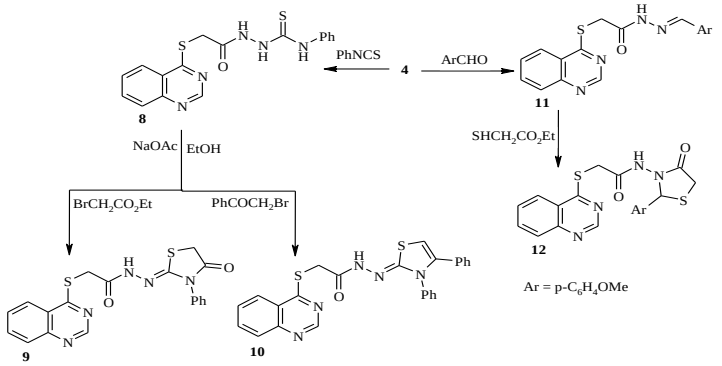
Sample Synthesis

The quinazoline-4-thiol (**1**), which is used as starting material in this study, was prepared according to the reported method [15]. The thiol **1** was alkylated with ethyl 2-chloroacetate and 2-chloroacetonitrile, in anhydrous DMF containing anhydrous potassium carbonate, to afford ethyl 2-(quinazolin-4-ylthio)acetate (**2**) and 2-(quinazolin-4-ylthio)acetonitrile (**3**) in good yields 87%, 77% respectively. Compounds **2** and **3** were treated with hydrazine hydrate, in ethanol, to give acid hydrazide **4** and amidrazone **5**. Cyclization of acid hydrazide **4** with CS_2 and KOH resulted to the formation of 5-((quinazolin-4-ylthio)methyl)-1,3,4-oxadiazole-2-thiol (**6**). Amidrazone derivative **5** was also treated with CS_2 in methanol to the thiol **7**. The structure of compounds **6** and **7** were established under the basis of their elemental analysis and spectral data (scheme 1).

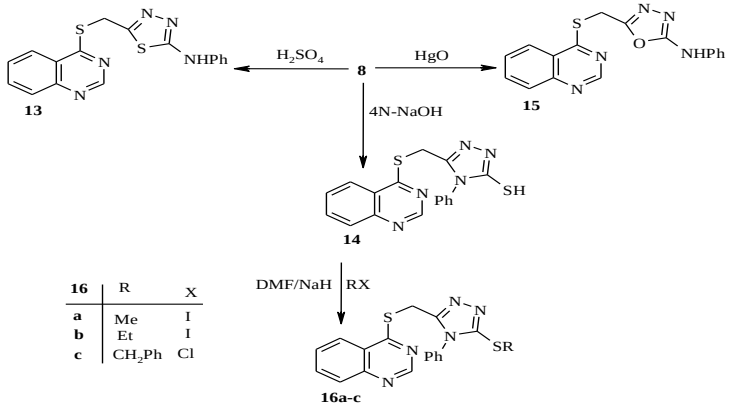


Scheme 1. Alkylation and formation of oxa- and thiadiazol of quinazoline-thiomethyl

Reaction of hydrazide **4** with phenyl isothiocyanate in absolute ethanol afforded thiosemicarbazide **8**, which was then treated with ethyl bromoacetate or phenacyl bromide, respectively. The mass spectrum of **8** showed peaks corresponding to its molecular ion peaks at *m/z* 370 (M^+ + 1) and 369 (M^+). The IR spectrum of **9** showed an absorption band at 1743 cm^{-1} due to the carbonyl function of thiazolidinone moiety. The ^{1}H NMR of **9** showed a singlet signal at 4.06 ppm corresponding to methylene protons of thiazolidene ring while ^{1}H NMR of compound **10** display one singlet at 6.03 ppm corresponding to thiazole ring protone. Also, condensation of acid hydrazide **4** with *p*-methoxy benzaldehyde yielded the corresponding hydrazide-hydrazone **11**, which on condensation with mercaptoacetic acid afforded 4-thiozolidinone **12**. The ^{1}H NMR spectrum of **12** showed signal N-H resonance at 11.01 ppm and methylene protons of the 4-thiazolidinone ring display two signals appearing as doublets at 3.83 and 3.87 ppm due to the non-equivalent, geminal methylene protons [23] interacting with the chiral center at position 2. This phenomenon was not observed with compound **9** lacking the asymmetric carbon. The methin proton of 4-thiozolidinone **12** showed resonance at 5.84 and methyl protons of methoxy function gave a singlet at 3.75 ppm (scheme 2).



Scheme 2. Synthesis of the thiazole derivatives.



Scheme 3. Cyclization reactions of thiosemicarbazide

When the thiosemicarbazide **8** was treated with sulfuric acid, 1,3,4-thiadiazole derivative **13** was formed in 71% yield. The preferred formation of the thiazdiazole ring under such acidic conditions can be due to the loss of nucleophilicity of N-4 as s result of its protonation leading to an increase in the nucleophilicity of the sulfur atom toward the attack of the carbonyl carbon. On the other hand, when the cyclization of **8** was carried out under alkaline conditions, the nucleophilicity of N-4 is enhanced and leads to cyclization with the carbonyl carbon atom to give the 1,2,4-triazole derivative **14** in good yield 90%. When the cyclization was performed by mercuric oxide, the 1,3,4-oxadiazole derivative **15** was formed in 85% yield. The mode of cyclization includes desulfurization by mercuric oxide, which introduces the oxygen atom in the cyclization process [24,25]. The structures of the obtained compounds **13-1**5 were elucidated by spectral analysis. In the ^{1}H

NMR spectra, the signal due to the S-CH_2 methylene protons present in all compounds **13-15** at 4.03-4.53 ppm, as singlets. NH and SH protons were observed at 10.06-10.58 and 14.01 ppm as broad singlets respectively. The thiol **14** was alkylated, after its treatment with 60% sodium hydride in anhydrous DMF, with methyl-, ethyl iodide and benzyl chloride to give the corresponding S-alkyl derivatives **16a-c**. Structures of the latter compounds **16a-c** were established on the basis of ^{1}H NMR spectra, which showed the absence of the characteristic SH peak at 14.01 ppm and the presence of signals, singlet at 2.49 ppm for S-Me, triplet at 1.33 ppm, quartet at 3.11 ppm due to the ethyl group, and singlet at 4.40 ppm due to the benzyl group respectively (scheme 3).

Radiation Dosimetric Activity

Figure 2, Figure 3 and Figure 4 show a typical TL glow curves of the compounds under investigation, irradiated with different low doses (0.5 Gy up to 2 Gy).This was acquired at heating rate of 2°Cs^{-1}.A good fit of the main glow peak can be obtained around 200°C.The local of the peak doesn't change by increasing the dose, just the response increase in linear relationship. The maximum peak height changes linearly with dose, which suggests detecting and monitoring the dose

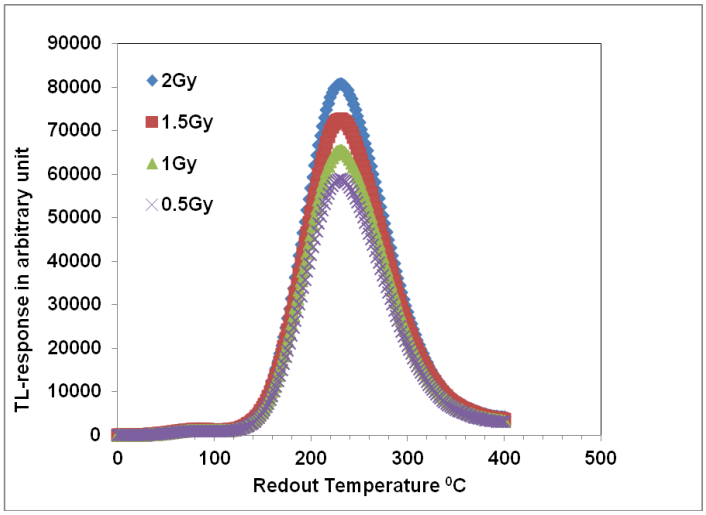


Figure 2: The Different Glow Curves for Different Doses for 1, 3, 4-Oxadiazole

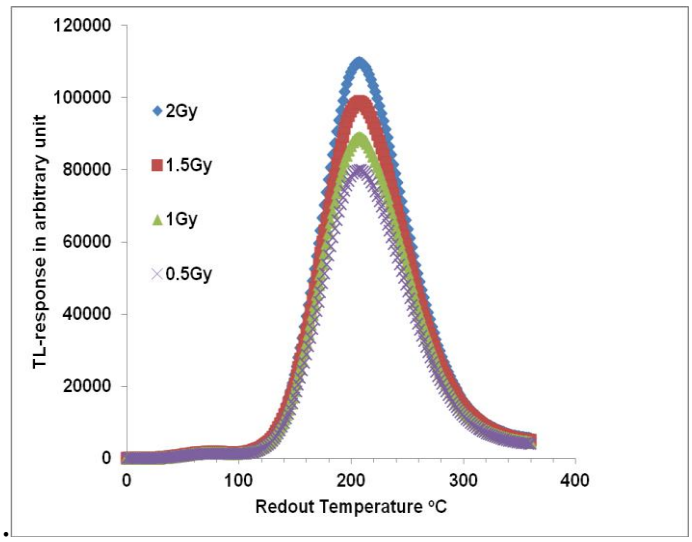


Figure 3: The Different Glow Curves for Different Doses for 1, 3, 4-Thiadiazole

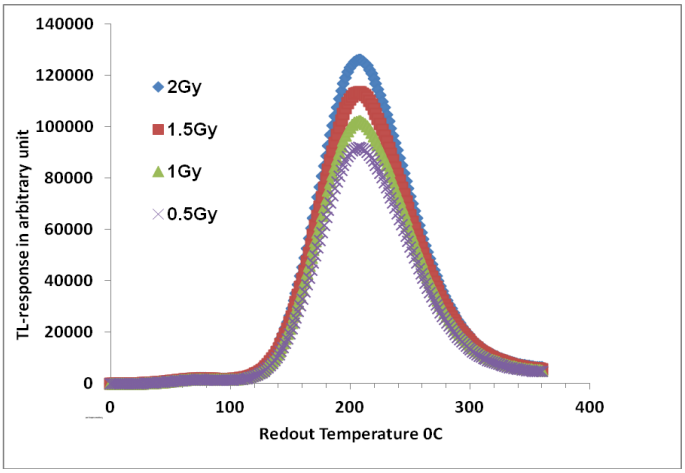


Figure 4: The Different Glow Curves for Different Doses for 1, 2, 4-Triazole

The peak is more dominant for all doses, it is a stable peak. The sensitivity of the dosimeter system including **11** is twice the value of compound **6** due to the large cross section of **11** which gives the wide area of traps.The broadness of the peak could be as a result of the existence of closely spaced trapping center for which individual glow peaks could not be resolved.This indicates a complex trapping system in compound and especially for substance doped with **11** impurities.It is better to express the results as peak heights since they show better spatial resolution than peaks areas due to smaller dissipation than peaks areas.It is important to stress the fact that the present TL results are characteristic of freshly samples.Therefore, one may expect a radically similar TL behavior for different annealing temperatures, mainly due to the similar precipitated.Trap parameters such as the activation energy (E), the order of kinetics (b) and the frequency factor (s) were calculated for the 200 ^{o}C main glow peak of the compound doped with different rare earth dopants oxides.Phosphor samples irradiated by gamma ray at 0.5 Gy up to 2 Gy doses and at 200 ^{o}C, using the method based on the shape of glow curves as proposed by Chen [26,27].

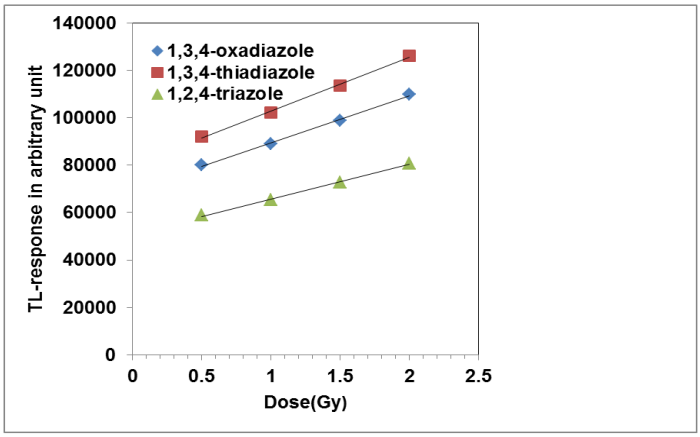


Figure 5: TL Response vs. Dose of 1, 3, 4-Oxadiazole, 1, 3, 4-Thiadiazole and 1, 2, 4-Triazole for Irradiation with ^{60}Co Photons. TL Response is Obtained as the Peak Height between 0°C and 360°C Divided by the Dose Rate

The relation between the different high & low doses and the TL-response as a peak height and integral value for material doped with **5**, **6**, **and 11** have been represented in Fig. 5.The response of the material doped with **5** was approximately twice value the response of doped with **6**.The host materials doped with **11** ions have a TL-sensitivity 100 bigger than the same materials doped with **6** ions. The host materials doped with **11** ions have a TL-response linear at high doses.The slope of the straight line is approximately one.

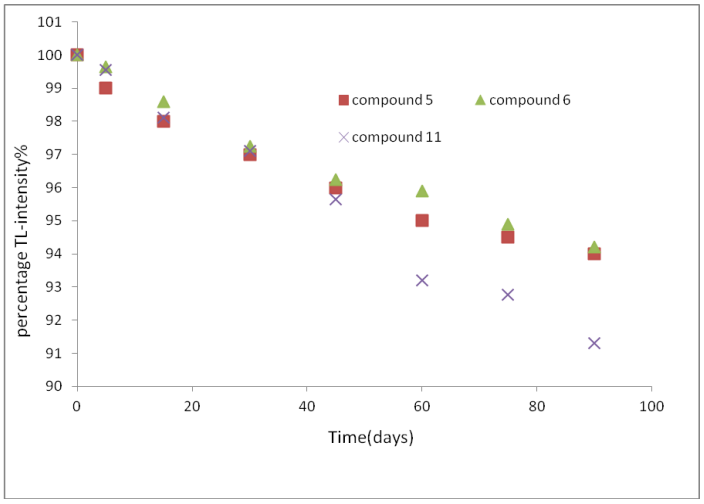


Figure 6: TL-Intensity of Different Dosimeter in Terms of Fading at Room Temperature

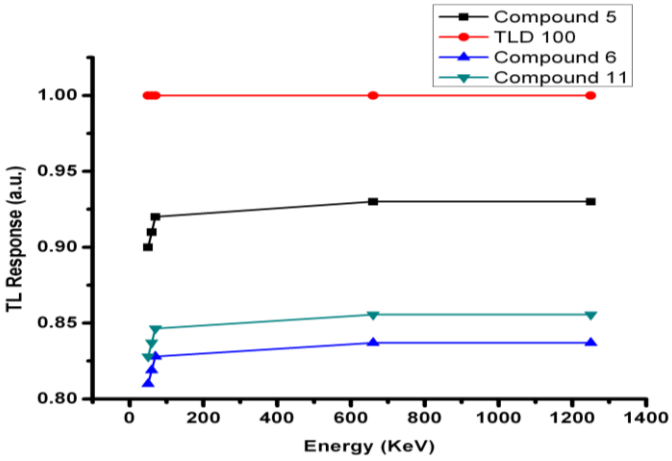


Figure 7: TL-Intensity of Different Dosimeters in Terms of Energy Dependence

The relative TL intensity was plotted as a function of gamma-ray irradiation dose for the telluride glasses phosphor sample as shown in Fig. 5**.**The TL dose dependence curve was observed to be linear in the dose range 0.5 Gy up to 2 Gy. In standard dosimetry, the integral over the glow curves up to about 200°C is used to determine the absorbed dose.The linear part of the curve is found to follow the relation Y = 1.25 X + b Where Y: is the TL-response in arbitrary units and X is the absorbed dose in (Gy).The b is the extrapolation to the Y axis which has a value equal: 360, a: is the slope which has a value equal to 1.25.From this relationship it is easy to measure the TL–response of the dosimeter and the absorbed dose can be calculated. Also the relative sensitivity of compounds is quite different for each type of detectors.

Figure 6 shows the integrated TL-intensity after storage period of three months for different materials systems used in TLD.The fading is high (equal 15%) due to the main **11** composition.The fading of **5** is less than the former; it is equal 8% after three months of storage at room temperature. In this paper, it is demonstrated that the fading of the given compounds cannot be explained only by the ionization of trapping centers.It must be considered the second process the diffusion of oxygen in compounds to explain the fading of compounds.Concerning the energy dependence of compounds prepares groups (as many points of energy as possible for one intends to use) of at least 6 TLDs each, irradiate each group with a reference dose at energy one.Fig. 7 shows the integrated TL-intensity after irradiation materials at 2 Gy with different radiation energies, the different compounds materials exhibit a steady state relationship with different energies at the same dose which predict the energy independent behavior of these materials.

The therapeutic dose range (0.5-2 Gy) of the TL response versus the delivered dose without reaching saturation level provides a possibility to use this material in a phantom for checking the treatment plans of the dose delivery in the near future.The results showed that the TL-radiation response was found to be sensitive to the compounds composition quantitatively and qualitatively due to different created trap centers according to the type of doping oxides.

CONCLUSIONS

New azole heterocycles were synthesized and their dosimetric properties of were investigated. From the obtained results it could be concluded that:

- The TL-radiation response was found to be sensitive to the compound composition quantitatively and qualitatively due to different created trap centers according to the type of doping oxides.
- The therapeutic range (0.5 to 2 Gy) of the TL response versus the delivered dose without reaching saturation level provides a possibility to use this material in a phantom for checking the treatment plans of the dose delivery in the near future.
- The TL enhancement response to gamma radiation makes the substance doped with **11**system a promising material for gamma detection dosimetry. These properties may have important applications in developing selective detectors and dosimeter suitable to study the biological effects of ionizing radiation exposure.
- The experiment results showed that for compounds investigation of thermoluminescence, the compound potential use as the materials of gamma-ray thermoluminescence.

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